EVALUATING PROTEIN DEGRADATION ENZYMES AND POST-TRANSLATIONAL MODIFICATION IN REGULATING α-SYNUCLEIN MISFOLDING IN YEAST

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Parkinson's disease is an incurable, fatal neurodegenerative illness that results from the selective death of midbrain dopaminergic neurons. Misfolding and aggregation of the protein α-synuclein, oxidative damage, and proteasomal impairment are current hypotheses of dopaminergic cell death. Yeasts are useful to evaluate α-synuclein biology and to characterize factors that regulate its misfolding and protect against its toxicity. In this study, a *Saccharomyces cerevisiae* model was used to evaluate regulation of misfolding and functional properties of wild-type and mutant (A30P, A53T, and A30P/A53T) forms of α-synuclein. In several yeast strains, wild-type and A53T mutant α-synuclein localized prominently near the plasma membrane, supporting known *in vitro* lipid-binding ability. In contrast, the A30P mutant was cytoplasmic while A30P/A53T showed membrane and cytoplasmic fluorescence. In yeast containing a partial mutant for the 20S' proteasomal barrel or its 19S' cap, delayed membrane association and increased foci formation was observed, respectively. Currently, we are examining E1, E2, and E3 enzyme specificity for regulating α-synuclein misfolding. Expressed α-synuclein migrated 6-8 kDa higher than predicted on denaturing gels and often in multiple monomeric bands, and a significant fraction was resistant to solubilization. We are testing whether post-translational modification (phosphorylation and nitrosylation) on α-synuclein misfolding underlies these behaviors. Yeast illustrate aspects of α-synuclein biology and pathology and serve as useful models for studying molecular mechanisms of misfolding linked to neurodegeneration. (NSF 0115919 and NIH NS48508).